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10/612,894	07/07/2003	James M. Hagberg	108172-00097	7034

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
11/05/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/612,894	HAGBERG ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *21-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending.
Claims 21-27 are withdrawn as detailed in the previous Office Action of 11/15/2006.
Claims 1-20 are examined on the merits

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08/20/2007 has been entered.

This Office Action is in reply to Applicants' correspondence of 08/20/2007.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

New Claim Objections

1. Claims 1, 7, and 13 are objected to because of the following informalities:

Claim 1 is objected to because the claim recites 'a subject', 'a human subject', and 'the subject' in the preamble, first step, and second step of the claim. For consistency the term 'subject' should be preceded by the term 'human' in each case.

Claims 1, 7, and 13 are objected to because the claims recites the term 'PA1-1' where the term 'PAI-1' is correct.

Claim 7 is objected to because the claim recites 'a human subject', 'a subject', and 'the subject' in the preamble, first step, and second step of the claim. For consistency the term 'subject' should be preceded by the term 'human' in each case.

Claim 7 recites the phrase 'at least one 1 allele' in the fourth line of the claims, where the phrase 'at least one I allele' is correct.

Claim 13 is objected to because the claim recites 'a human subject', 'a subject', and 'the subject' in the preamble, first step, and second step of the claim. For consistency the term 'subject' should be preceded by the term 'human' in each case.

Appropriate correction is required.

New Objection to the Specification – New Matter

2. The amendment filed 08/25/2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment to ¶ [0021] of the specification changes the explicit definition of the phrase 'limited exercise'. In the originally filed specification, the definition of the phrase encompasses exercise that includes about 5 single courses of exercise (i.e. 'about 5 single courses of exercise'). The definition of the phrase 'limited exercise' as amended recites 'less that about 5 single courses of exercise', where the amended

definition thus specifically excludes one of the alternatives recited in the originally filed definition of the phrase (i.e. exercise of 'about 5 single courses of exercise' is specifically excluded because the 'limited exercise' must be 'less than about 5'). As such, the explicit definition of 'limited exercise', with the specific exclusion of 'about 5 single course of exercise', is not supported by the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Furthermore, it is noted that MPEP 608.04(c) states:

> Where the new matter is confined to amendments to the specification, review of the examiner's requirement for cancellation is by way of petition. But where the alleged new matter is introduced into or affects the claims, thus necessitating their rejection on this ground, the question becomes an appealable one, and should not be considered on petition even though that new matter has been introduced into the specification also. 37 CFR 1.181 and 37 CFR 1.191 afford the explanation of this seemingly inconsistent practice as affecting new matter in the specification.

Withdrawn Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

3. The rejection of claims 1-20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention over recitation of the parenthetical term '(t-PA)' in claims 1, 7, and 13 with the explanation of the abbreviation as 'tissue plasminogen activator', is **WITHDRAWN** in light of the amendments to the claims.

Maintained Claim Rejections - 35 USC § 112 1st¶ - New Matter

The following rejection is a NEW REJECTION necessitated by Applicant's amendment to the claims.

4. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

5. The claims of the instant application are drawn to a method of increasing fibrinolysis in a subject comprising the identification of subjects with particular PAI-1 alleles **and** particular alleles at the t-PA gene locus. However, the instant specification does not provided a basis for the identification of individuals with specific PAI alleles and specific t-PA alleles in a method of increasing fibrinolysis by engaging the subject in exercise.

The specification indicates that the invention is directed to a method comprising 'identifying a subject having an allele and/or genotype at **a** particular gene locus' (emphasis added, which indicates the analysis of alleles in a single gene) (specification ¶[0006]). The specification further indicates that the 'inventors have investigated the plasminogen activator inhibitor-I (PAI-1) gene promoter site, in particular genotypes 4G/5G, 4G/4G, and 5G/5G' (specification ¶[0011]).

While the specification provides some data regarding the association of I and D t-PA genotypes with t-PA activity and antigen levels in response to exercise, the specification does not specifically contemplate the use of PAI genotype **in combination with** t-PA genotype in an individual as indicative of increased fibrinolysis in response to exercise.

Response to Remarks

Applicants have traversed the rejection of claims for new matter indicating that (p.5 of Remarks) one of skill in the art would understand the benefits of looking at both genotypes (PAI and t-PA) together, based on the combination of Tables I and II in the specification. This argument is not found to be persuasive. The specification provides no example of, or specific contemplation of, using the combination of PAI and t-PA genotypes in a single individual for the prediction of response to exercise. The specification does not, for example, provide any guidance on how the particular genotypes of the different genes would, in combination, effect the required phenotype of fibrinolysis in response to exercise.

The rejection is **MAINTIANED.**

Newly Presented Claim Rejections - 35 USC § 112 1st¶ - New Matter

The following rejection is a NEW REJECTION necessitated by Applicant's amendment to the specification which changes the definition of the phrase 'limited exercise'.

6. Claims 6, 12, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

7. The claims of the instant application are drawn to a method of increasing fibrinolysis in a subject comprising engaging a subject in 'limited exercise'. As defined

by the specification, as amended by the amendment of 08/25/2006, the definition of 'limited exercise' specifically excludes exercise comprising 'about 5 single courses of exercise', where the originally filed specification provides a definition of 'limited exercise' that encompasses 'about 5 single courses of exercise'.

Maintained Claim Rejections - 35 USC § 112

This rejection contains new grounds of rejection as necessitated by Applicants' amendments to the claims.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not provide a method to increase fibrinolysis, prevent cardiovascular disease, or ameliorate cardiovascular disease in a subject, for which the PAI-1 gene promoter and t-PA gene locus genotype has been determined, using exercise.

Nature of the Invention and Breadth of the Claims

The specification asserts that the instant invention relates to identifying genetic markers that correlate with improved success in increasing fibrinolysis levels in subjects through exercise training (paragraph [0003]). The claims are drawn to methods for

effecting change in subjects with particular genotypes at the PAI-1 gene promoter polymorphic site using exercise training. Claims 1-6, 18 and 20 are drawn to methods for increasing fibrinolysis in a subject. Claims 7-12 are drawn to methods for preventing cardiovascular disease in a subject. Claims 13-18 are drawn to methods for ameliorating cardiovascular disease in a subject.

The claims encompass subjects with at least one 4G allele (i.e. both homozygous 4G/4G subjects and heterozygous 4G/5G subjects) (claims 1, 4-7, 10-13, 16-20), subjects with heterozygous (i.e. 4G/5G) genotypes (claims 2, 8, and 14), and subjects with homozygous 4G/4G genotypes (claims 3, 9, and 15). The claims encompass exercise regimens comprised of extensive exercise (claims 4, 10, and 16), moderate exercise (claims 5, 11, and 17), and limited exercise (claims 6, 12, and 18). Claim 19 requires that the subject is homozygous for the t-PA I allele, and claim 20 requires that the subject is heterozygous (I/D) for the t-PA allele.

The claims encompass any subject organism that contains the PAI-1 gene.

The nature of the invention requires knowledge of a correlation between the specific PAI-1 gene promoter and t-PA genotypes of a subject and the response (with regard to fibrinolysis levels) of that subject to exercise training.

Direction provided by the specification and working example

The specification teaches an example in which subjects were analyzed for several parameters indicative of fibrinolysis levels (i.e. PAI-1 and t-PA activities and t-PA antigen (paragraph [0031]) prior to participation in an exercise program to establish baseline values, and then after participation in an exercise program (paragraph [0045]).

The specification further teaches the genotyping of the PAI-1 gene promoter with respect to the 4G/5G polymorphic site (paragraph [0042]) by PCR amplification followed by restriction enzyme analysis of the resulting amplicon.

The instant specification provides an analysis of the changes in the measured parameters among the three possible (4G/4G; 4G/5G; 5G/5G) PAI-1 genotypes. The data indicate the following results: the average PAI-1 activity decreased for the 4G/4G and 5G/5G groups, and increased for the 4G/5G group; the average t-PA activity increased for all groups; the average t-PA antigen decreased for all groups. While the specification asserts that there is a tendency for subjects with 4G/4G genotypes to respond better than subjects with 4G/5G or 5G/5G genotypes (paragraph [0048]), the analysis of the data (P ANOVA) indicates that none of the changes are statistically significant.

The specification further teaches an analysis of the changes in t-PA activity and t-PA antigen among the three t-PA genoptypes (I/I; I/D; D/D). The data indicate the following results: the average PAI-1 activity increased for the I/I and I/D groups, and decrease for the D/D group; the average t-PA antigen decreased for the I/I and I/D groups, and increased for the D/D group. The analysis of the data (P ANOVA) indicates that none of the changes are statistically significant.

The instant specification does not provide any data concerning any sort of control group, for example a reference group that did not participate in an exercise program.

The specification asserts that improving fibrinolysis prevented the development of cardiovascular disease or alleviated symptoms of cardiovascular disease (paragraph

[0007]). There is no indication that either of these two qualities was actually measured in any of the analyzed subjects; Example 1 indicates that subjects were in fact excluded from the study if they had cardiovascular disease.

The specification does not provide any examples in which the genotype of a subject was identified at both the PAI-1 promoter and the t-PA gene locus.

The specification presents results only from a population of human male and female subjects age 50-70.

The specification presents results only from participation in moderate exercise training (paragraph [0047], Table 1). The specification provides no results from subjects that participated in extensive exercise, or subjects that were involved only in limited exercise.

State of the art, level of skill in the art, and level of unpredictability

The level of skill in the art with regard to identification of PAI-1 gene promoter and t-PA genotypes is high, however the prior art and the instant specification shows that the level of unpredictability in correlating any particular individual's genotype with fibrinolysis levels in response to exercise is high.

Väisänen et al teaches an analysis of fibrinolytic activity response to exercise among groups of subjects with different PAI-1 gene promoter genotypes. Although the Väisänen reference was applied to the art rejection earlier in this Office Action, the reference is cited in this enablement rejection to demonstrate the state of the art and its unpredictability; the specification of the instant application cannot be considered enabling for the methods of Väisänen because the instant application does not present

the same data, gathered from the same population, as Väisänen. The Väisänen reference indicates that PAI-1 activity decreases (thus an indicator of increased fibrinolysis) in subjects from all subject groups regardless of PAI-1 genotype, as well as in reference groups (who do not participates in exercise) with both the 4G/4G and 4G/5G genotypes (Table 1). While the reference indicates that only the decrease in PAI-1 activity seen in the 4G/4G exercise group is significant (p=0.025; Table 1), the reference also indicates that the findings need to be replicated in other controlled randomized exercise studies (p.1119, right col., lns.52-53).

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis is illustrated by the instant specification. Table 1 (paragraph [0047]) indicates p-values from ANOVA analysis of several fibrinolysis related parameters that range from 0.189 to 0.802. Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of p=0.05 would not be considered strong enough for the basis of a conclusion.

The unpredictability of associating PAI-1 genotype with exercise-induced increases in fibrinolysis is further exemplified by Tiyasangthong (2001). Tiyasangthong examine the hypothesis that exercise training effects fibrinolytic variables (p.103), and that the changes in PAI-1 activity with exercise training is related to PAI-1 polymorphisms (p.107). The reference indicates that there is no statistically significant

correlation in changes in the measures of fibrinolytic parameters (PAI-1 and t-PA activity, and t-PA antigen) with regard to PAI-1 gene promoter genotype (p.95; p.96, Table 7).

With regard to the analysis of the t-PA I/D allele, the unpredictability of using this allele as a predictor of fibrinolysis in response to exercise training is demonstrated by the data of the instant specification. For example, the data of Table 2 indicates that there is no significant association between fibrinolysis in response to exercise (as measured by t-PA activity or t-PA antigen) and t-PA genotype of an individual. The specification indicates that t-PA antigen is decreased in subjects with t-PA genotypes I/I and I/D, which given the definition of 't-PA antigen' provided in the specification where 't-PA antigen' is 'the t-PA composition that stimulates fibrinolysis' (specification ¶[0013]), would seem to indicate that decreased t-PA antigen is indicative of decrease t-PA activity and thus decreased fibrinolysis. However, a measure of t-PA antigen is in fact not a measure of fibrinolysis, merely a measure of the amount of t-PA antigen present in a blood sample, whereas actual t-PA activity is required for fibrinolysis. Additionally, although t-PA antigen is not a measure of fibrinolysis, the data of table 2 indicates that the P ANOVA of t-PA genotype associated with t-PA antigen is 0.054 which is not statistically significant. The prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the

conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion.

Furthermore, claims drawn to methods for preventing cardiovascular disease may be considered as encompassing those methods which completely keep even the most minor forms of cardiovascular disease from occurring; wherein the pertinent method step is engaging a subject in exercise training. And while there may be an inverse relationship between physical activity and the risk of developing cardiovascular disease, the prior art of Sesso et al (2000) indicates that participation in physical exercise is not sufficient to provide a guaranteed prevention of any form or type of cardiovascular disease (Table 2; p.976, right col., lns.44-53).

Quantity of experimentation required

There would be a large amount of experimentation required to make and use the claimed invention. In order to establish that there is any statistically significant association between PAI-1 gene promoter and t-PA gene genotype and response to exercise, one would have to conduct a large case-control randomized study to compare fibrinolytic activity among subjects with different PAI-1 and t-PA gene genotypes upon exposure to exercise training. Such a study may or may not indicate that there is a reliable and statistically significant exercise dependent increase in fibrinolytic activity, prevention of cardiovascular disease, or amelioration of cardiovascular disease, that is associated with a subject's PAI-1 and t-PA genotype in any particular population.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and the breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the amount of guidance by the applicant and the paucity of working examples, it is the conclusion the an undue amount of experimentation would be required to make and use the invention claimed invention.

Response to Remarks

10. Applicant has traversed the rejection of claims under 35 USC 112 1st¶ for lack of enablement. Applicants' argue (p.5 of Remarks) that one reading the specification would certainly and immediately understand the disclosure and the benefit of looking at both genotypes together in deciding which human subjects would benefit from increased exercise to increase fibrinolysis, based on the combination of Tables I and II. The argument has been considered but is not found to be persuasive.

As set forth in the rejection, none of the P-values presented in specification are less than the 0.05 value required for statistical significance; there is in fact no example of identifying both the PAI-1 genotype and the t-PA genotype of any individual, and measure of t-PA activity is not a measure of fibrinolysis.

For the reasons set forth in the rejection, the examiner maintains that none of the data presented in the instant specification indicates a statistically significant association ($p<0.05$) between PAI-1 and t-PA genotypes and exercise-induced increase fibrinolysis. Thus the data of the instant specification do not teach a reliable method for increasing

fibrinolysis of a subject by identifying the PAI-1 and t-PA genotype of the subject and engaging the subject in exercise.

The rejection is MAINTAINED.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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